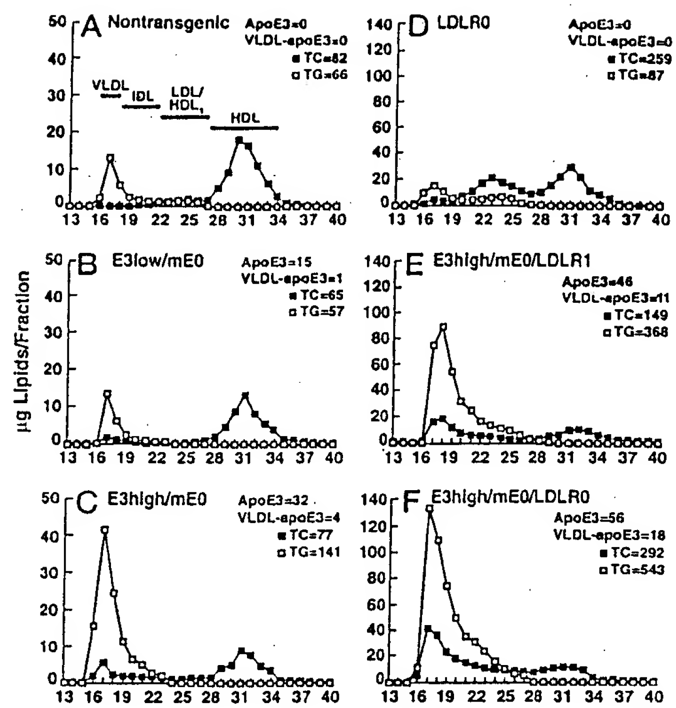

A Nontransgenic
ApoE3=0
VLDL-apoE3=0
TC=82
TG=66
VLDL
IDL
LDL/
HDL1
HDL
B E3low/mE0
ApoE3=15
VLDL-apoE3=1
TC=65
TG=57
C E3high/mE0
ApoE3=32
VLDL-apoE3=4
TC=77
TG=141
D LDLR0
ApoE3=0
VLDL-apoE3=0
TC=259
TG=87
E E3high/mE0/LDLR1
ApoE3=46
VLDL-apoE3=11
TC=149
TG=368
F E3high/mE0/LDLR0
ApoE3=56
VLDL-apoE3=18
TC=292
TG=543
μg Lipids/Fraction
13 16 19 22 25 28 31 34 37 40

FIG. 1

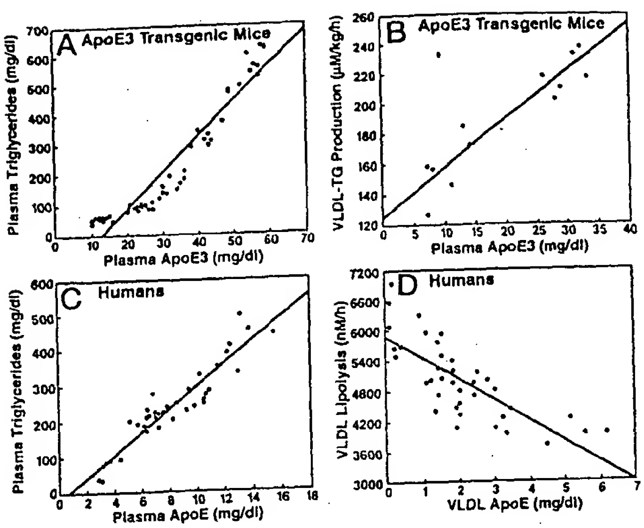

A ApoE3 Transgenic Mice
Plasma Triglycerides (mg/dl)
Plasma ApoE3 (mg/dl)
B ApoE3 Transgenic Mice
VLDL-TG Production (µM/kg/h)
Plasma ApoE3 (mg/dl)
C Humans
Plasma Triglycerides (mg/dl)
Plasma ApoE (mg/dl)
D Humans
VLDL Lipolysis (nM/h)
VLDL ApoE (mg/dl)

FIG. 2

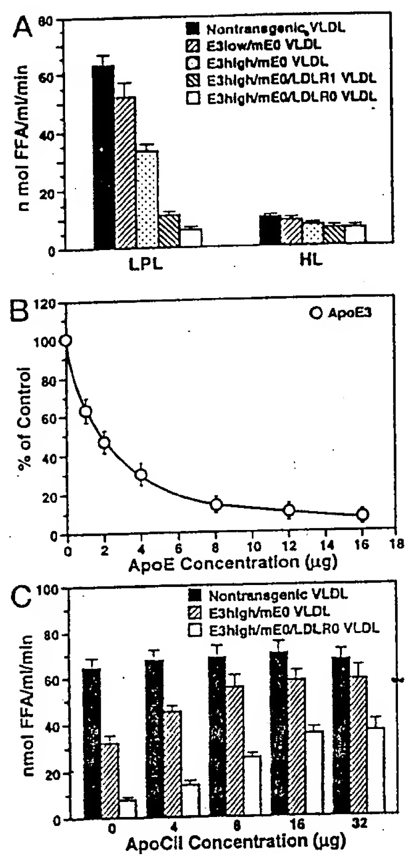
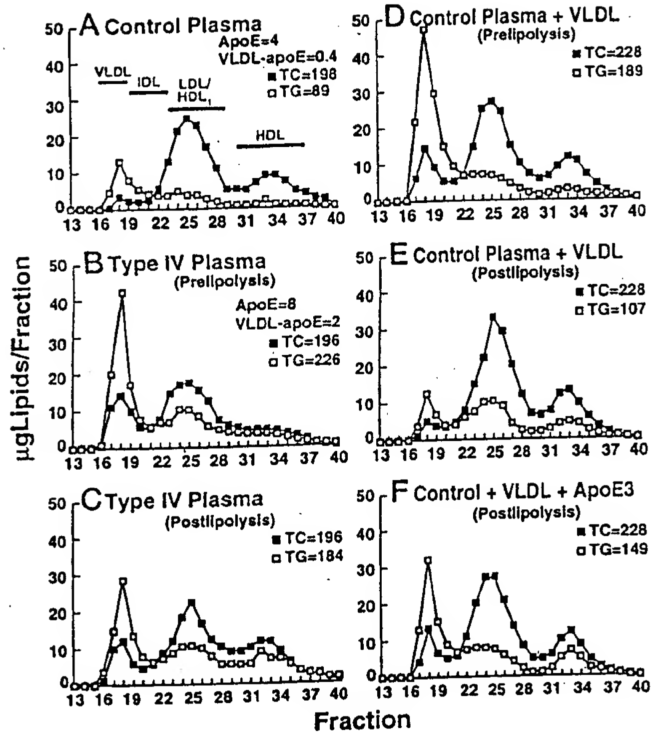

A
Nontransgenic VLDL
E3low/mE0 VLDL
E3high/mE0 VLDL
E3high/mE0/LDLR1 VLDL
E3high/mE0/LDLR0 VLDL
n mol FFA/ml/min
LPL
HL
B
ApoE3
% of Control
ApoE Concentration (µg)
C
Nontransgenic VLDL
E3high/mE0 VLDL
E3high/mE0/LDLR0 VLDL
nmol FFA/ml/min
ApoCII Concentration (µg)

FIG. 3



A Control Plasma
ApoE=4
VLDL-apoE=0.4
TC=198
TG=89
VLDL
IDL
LDL/HDL1
HDL
D Control Plasma + VLDL
(Prelipolysis)
TC=228
TG=189
B Type IV Plasma
(Prelipolysis)
ApoE=8
VLDL-apoE=2
TC=196
TG=226
E Control Plasma + VLDL
(Postlipolysis)
TC=228
TG=107
C Type IV Plasma
(Postlipolysis)
TC=196
TG=184
F Control + VLDL + ApoE3
(Postlipolysis)
TC=228
TG=149
μgLipids/Fraction
Fraction

FIG. 4

TABLE I

Lipid and apoE levels in plasma and VLDL from different lines of mice

Mice were in a mixed genetic background (C57BL6/ICR) and analyzed at 2–4 months of age. TC, total cholesterol; TG, triglycerides; E3, human apoE3; mE, mouse apoE; LDLR, LDL receptor; mE0, homozygous mouse apoE knockout; LDLR1, heterozygous LDL receptor knockout; LDLR0, homozygous LDL receptor knockout.

Mice	Plasma					VLDL				VLDL-TG production rate
	n	Human apoE3	Mouse apoE	TC	TG	*n*	Human apoE3	Mouse apoE	ApoC-II	
			mg/dl					*μg/mg*		*μM/h/kg*
Nontransgenic	18	0	7 ± 2	79 ± 10	47 ± 20	6	0	19 ± 4	32 ± 6	148 ± 18
E3low/mE0	12	13 ± 2	0	60 ± 6[a]	54 ± 10	6	23 ± 5	0	26 ± 5	168 ± 19
E3high/mE0	15	30 ± 4	0	78 ± 19	128 ± 36[a]	6	38 ± 5	0	13 ± 2[a]	221 ± 11[a,b]
LDLR1	19	0	10 ± 3	134 ± 14[a]	55 ± 18	6	0	24 ± 6	25 ± 5	
E3low/mE0/LDLR1	13	17 ± 2	0	136 ± 10[a]	62 ± 17					
E3high/mE0/LDLR1	17	45 ± 4	0	148 ± 14[a]	361 ± 69[a,c]	6	46 ± 4	0	7 ± 1[a,c]	
LDLR0	15	0	15 ± 3[a]	255 ± 34[a]	86 ± 19[a]	6	0	30 ± 7[a]	20 ± 3[a]	
E3low/mE0/LDLR0	9	23 ± 3	0	261 ± 11[a]	89 ± 18[a]					
E3/high/mE0/LDLR0	16	54 ± 4	0	294 ± 37[a]	532 ± 59[a,d]	6	55 ± 7	0	3 ± 1[a,d]	199 ± 16[a]

[a] $p < 0.01$ *versus nontransgenic mice.*

[b] $p < 0.05$ *versus* hE3low/mE0 mice.

[c] $p < 0.01$ *versus* LDLR1 mice.

[d] $p < 0.01$ *versus* LDLR0 mice.

FIG. 5

TABLE II

Effect of apoE expression levels of VLDL triglyceride production in McA-RH7777 cells stably transfected with various apoE isoforms

Values are means of duplicate experiments.

Cell lines	ApoE in medium		VLDL triglyceride secretion	
	Human apoE	Mouse apoE	Without heparinase	With heparinase
	ng/mg cell protein/h		*dpm/mg cell protein/4 h*	
McA-RH7777	0	353	5273	5604
McA-Neo	0	368	5451	5719
McA-apoE2–1	309	321	5193	6682
McA-apoE2–2	1210	332	3277	8828
McA-apoE2–3	2200	364	2103	11576
McA-apoE3–1	338	327	1958	6223
McA-apoE3–2	1237	339	1640	7815
McA-apoE3–3	2436	345	818	9896
McA-apoE4–1	318	368	2878	6540
McA-apoE4–2	1153	347	2491	8224
McA-apoE4–3	2192	355	832	10924

FIG. 6

Table III

Lipid and apoE levels in plasma and VLDL from normal or type IV hyperlipidemic human subjects

VLDL cholesterol and triglyceride and HDL cholesterol were calculated from the Superpose 6 chromatography profiles of plasma lipoproteins by summing the individual fractions (Fig. 4, *A* and *B*). FFA, free fatty acids; TC, total cholesterol; TG, triglycerides.

Exp.	Plasma							VLDL		VLDL lipolysis
	n	ApoE	TC	VLDL-TC	HDL-TC	TG	VLDL-TG	ApoE	ApoC-II	
				mg/dl				*μg/mg TG*		*nmol FFA/h*
I. Plasma sample comparisons										
Normolipidemic control	6	3.3 ± 0.6	193 ± 14	6 ± 2	54 ± 4	69 ± 27	22 ± 10	13 ± 3	39 ± 7	6068 ± 579
Type IV-1 200 < TG < 300)	19	8.2 ± 1.9[a]	204 ± 27	49 ± 7[a]	37 ± 7[a]	237 ± 24[a]	105 ± 13[a]	24 ± 3[a]	18 ± 3[a]	4888 ± 524[a]
Type IV-2 300 < TG < 400)	4	11.1 ± 0.9[a]	221 ± 25	66 ± 3[a]	34 ± 3[a]	348 ± 27[a]	152 ± 12[a]	30 ± 2[a]	13 ± 2[a]	4252 ± 353[a]
Type IV-3 (TG > 400)	4	13.6 ± 1.3[a]	254 ± 15[a]	76 ± 9[a]	33 ± 6[a]	447 ± 36[a]	200 ± 23[a]	37 ± 2[a]	10 ± 2[a]	3741 ± 214[a]
II. Effects of apolipoproteins on lipolysis										
Control + apoE3[b]	6	14.0 ± 0[a]						31 ± 3[a]	11 ± 1[a]	4132 ± 414[a]
Type IV-2 + apoCII[c]	4									5598 ± 198

[a] $p < 0.01$ *versus* control.

[b] Purified human apoE3 was added to control human plasma at a final concentration of 14 mg/dl. After incubation at 37 °C for 20 min, VLDL were isolated and analyzed for apoE content and LPL-mediated lipolysis.

[c] Purified human apoC-II (16 μg) was added to VLDL (30 μg of triglycerides) isolated from plasma of Type IV-2 subjects and its effect on LPL-mediated lipolysis was determined.

FIG. 7

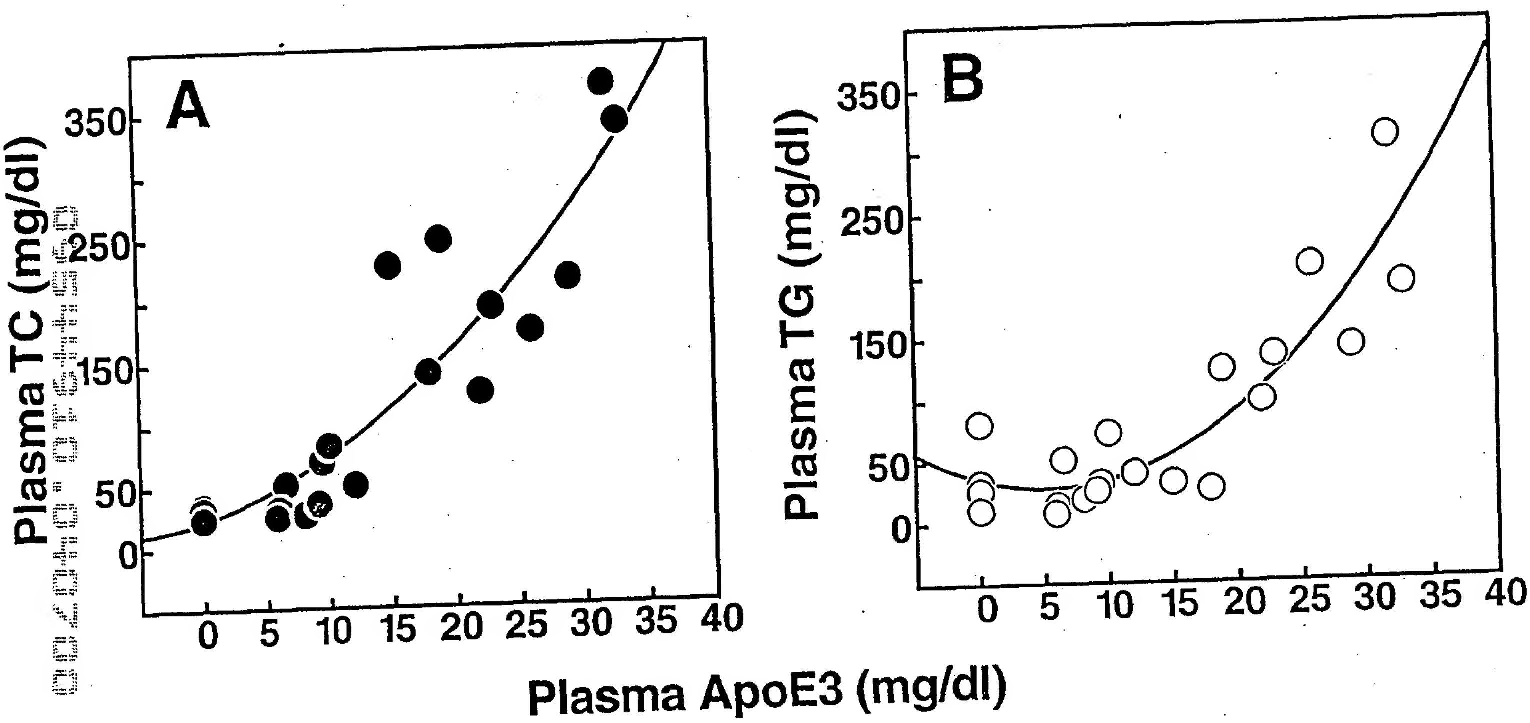

A
Plasma TC (mg/dl)
0
50
150
250
350
0 5 10 15 20 25 30 35 40
B
Plasma TG (mg/dl)
0
50
150
250
350
0 5 10 15 20 25 30 35 40
Plasma ApoE3 (mg/dl)

FIG. 8

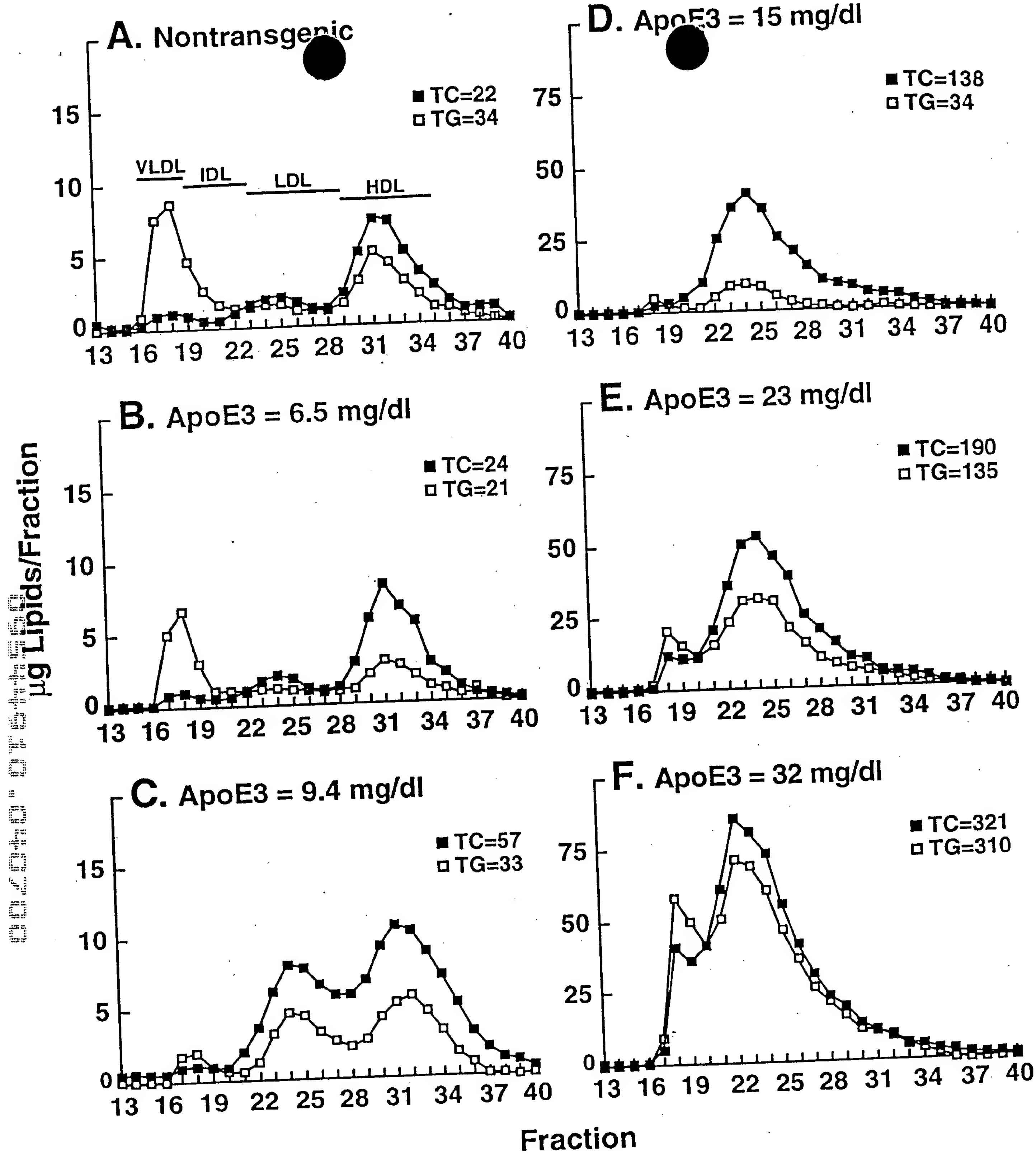

A. Nontransgenic
TC=22
TG=34
VLDL
IDL
LDL
HDL
D. ApoE3 = 15 mg/dl
TC=138
TG=34
B. ApoE3 = 6.5 mg/dl
TC=24
TG=21
E. ApoE3 = 23 mg/dl
TC=190
TG=135
C. ApoE3 = 9.4 mg/dl
TC=57
TG=33
F. ApoE3 = 32 mg/dl
TC=321
TG=310
μg Lipids/Fraction
Fraction

FIG. 9

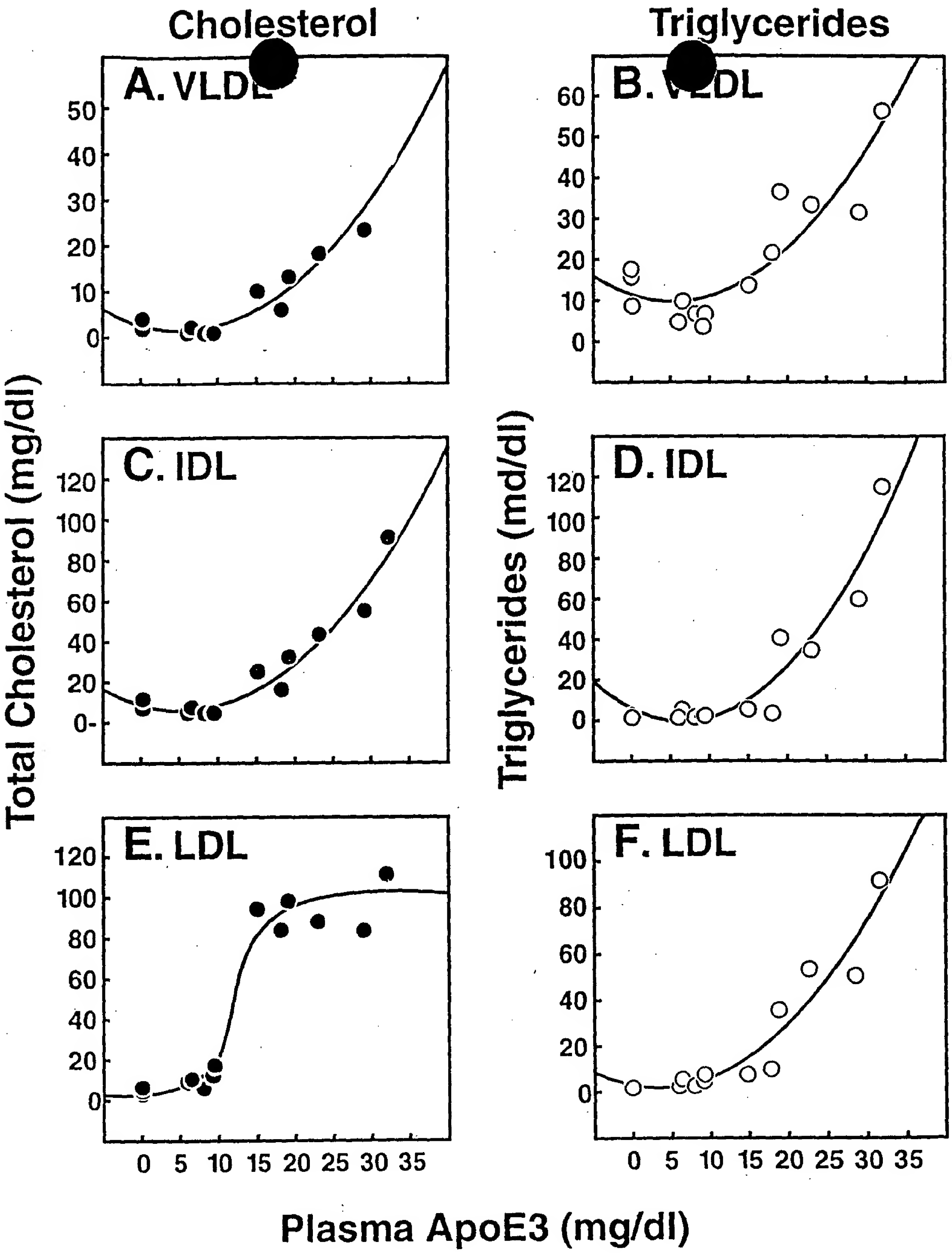
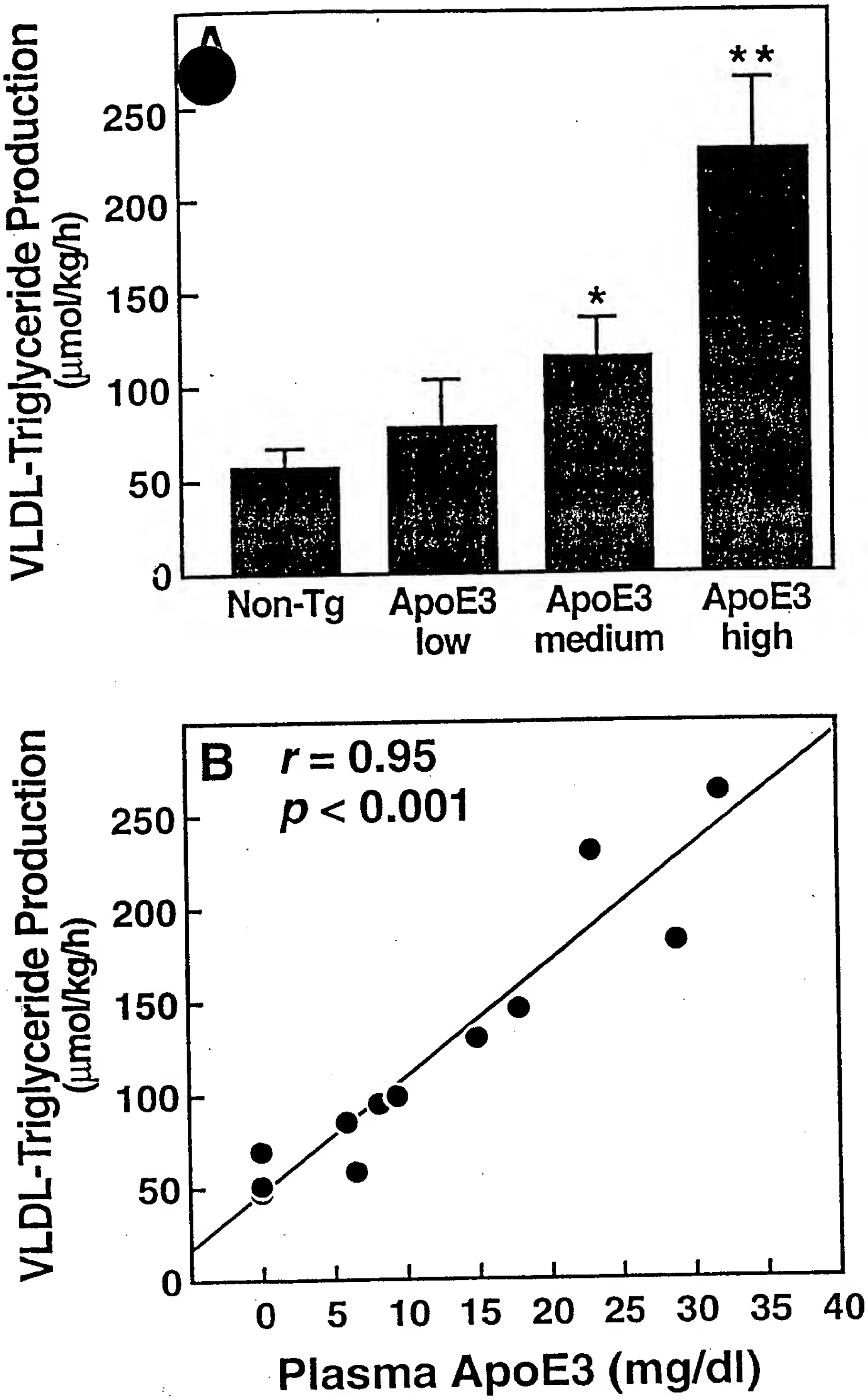

Cholesterol
Triglycerides
A. VLDL
B. VLDL
C. IDL
D. IDL
E. LDL
F. LDL
Total Cholesterol (mg/dl)
Triglycerides (md/dl)
Plasma ApoE3 (mg/dl)

FIG. 10



A
VLDL-Triglyceride Production
(µmol/kg/h)
0
50
100
150
200
250
*
**
Non-Tg
ApoE3 low
ApoE3 medium
ApoE3 high
B
r = 0.95
p < 0.001
VLDL-Triglyceride Production
(µmol/kg/h)
0
50
100
150
200
250
0
5
10
15
20
25
30
35
40
Plasma ApoE3 (mg/dl)

FIG. 11

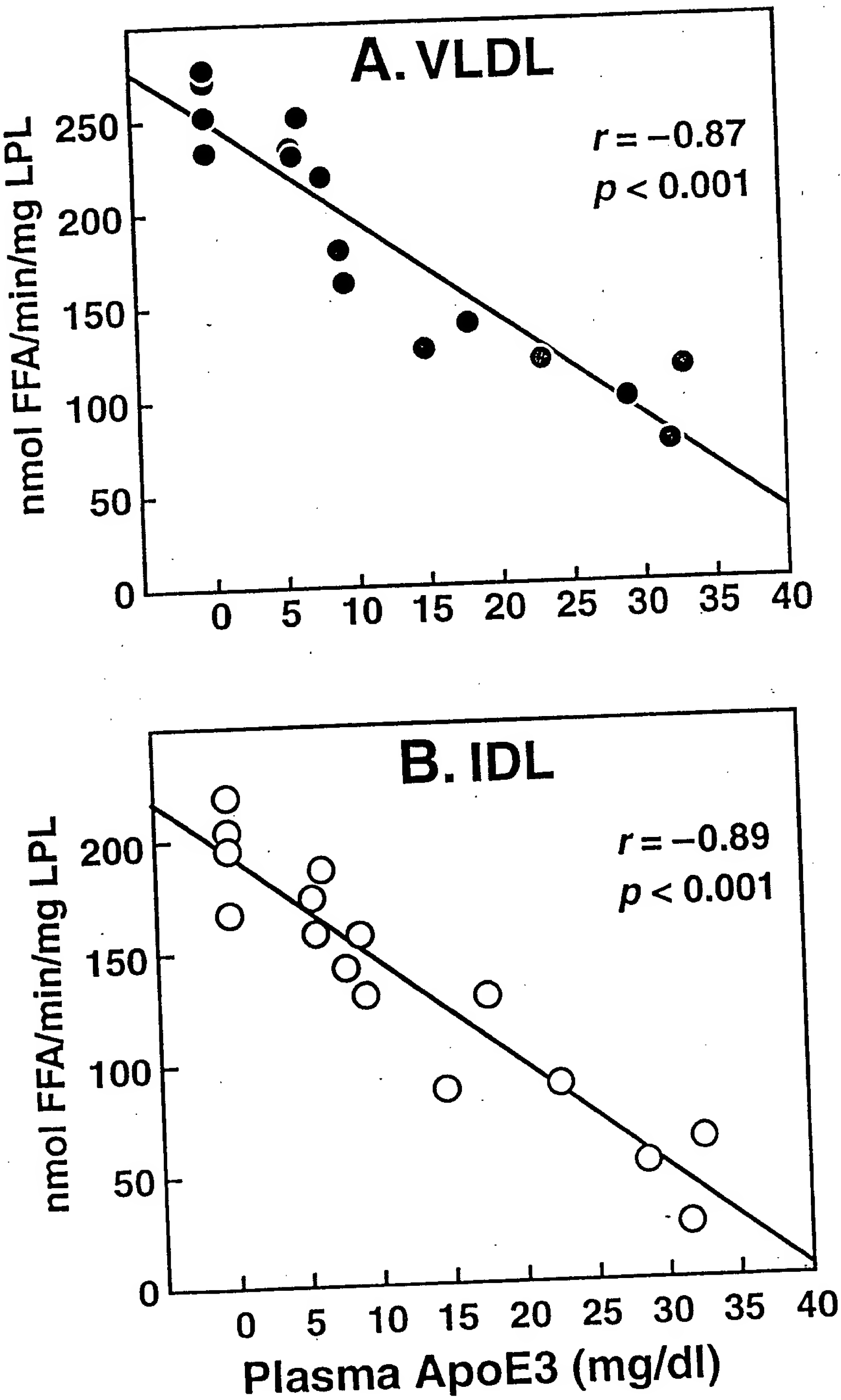

A. VLDL
r = −0.87
p < 0.001
nmol FFA/min/mg LPL
250
200
150
100
50
0
0
5
10
15
20
25
30
35
40
B. IDL
r = −0.89
p < 0.001
nmol FFA/min/mg LPL
200
150
100
50
0
0
5
10
15
20
25
30
35
40
Plasma ApoE3 (mg/dl)

FIG. 12

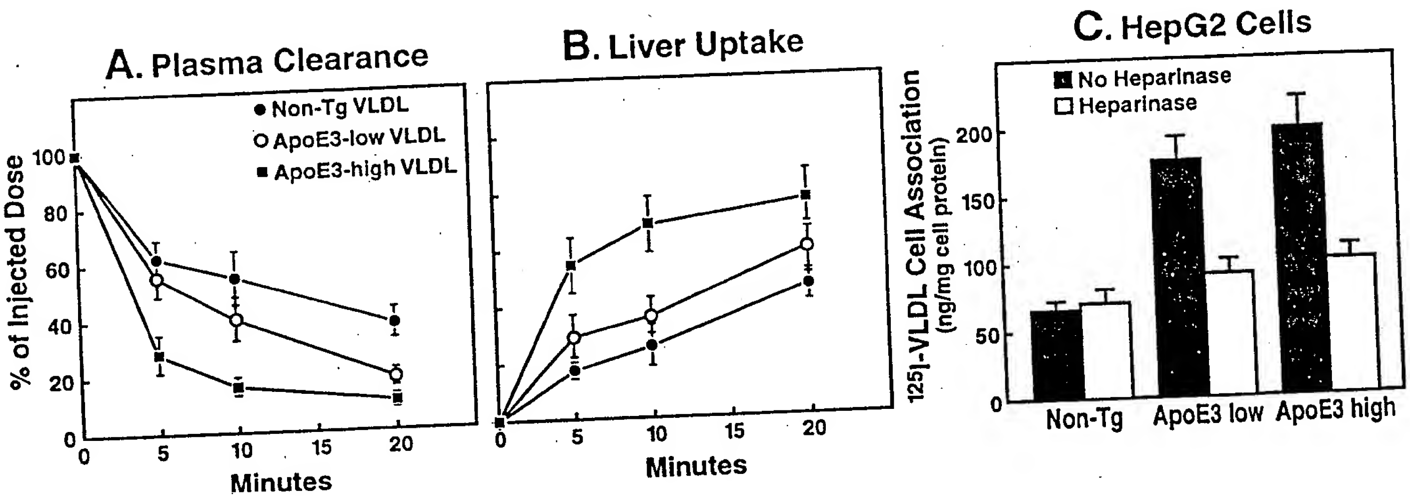

A. Plasma Clearance
Non-Tg VLDL
ApoE3-low VLDL
ApoE3-high VLDL
% of Injected Dose
100
80
60
40
20
0
0
5
10
15
20
Minutes
B. Liver Uptake
0
5
10
15
20
Minutes
C. HepG2 Cells
No Heparinase
Heparinase
125I-VLDL Cell Association
(ng/mg cell protein)
200
150
100
50
0
Non-Tg
ApoE3 low
ApoE3 high

FIG. 13

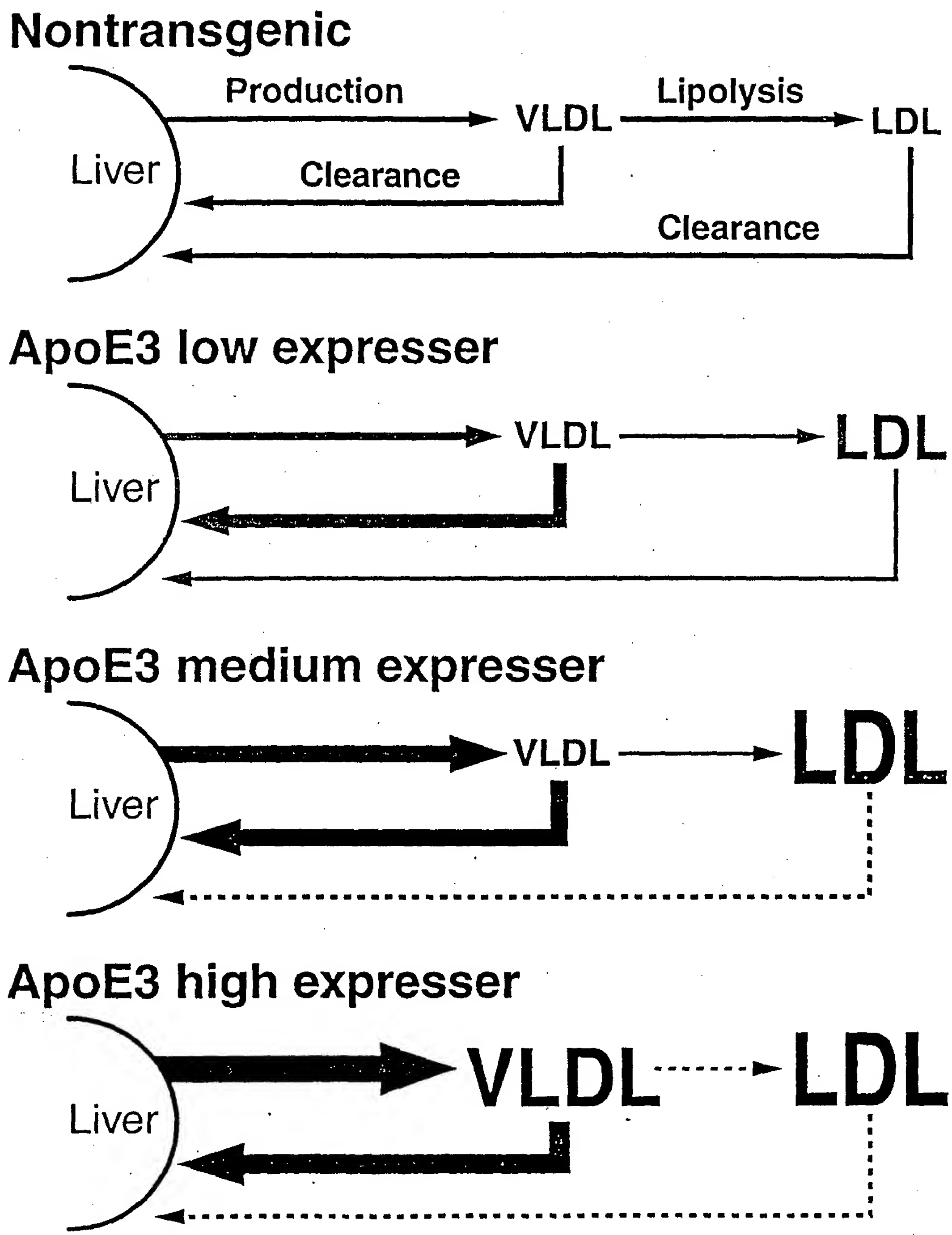

Nontransgenic
Production
VLDL
Lipolysis
LDL
Liver
Clearance
Clearance
ApoE3 low expresser
VLDL
LDL
Liver
ApoE3 medium expresser
VLDL
LDL
Liver
ApoE3 high expresser
VLDL
LDL
Liver

FIG. 14

TABLE IV

Plasma Lipid Levels of ApoE3 Transgenic Rabbits

Rabbits were analyzed at 8–12 months of age. TC, total cholesterol; TG, triglyceride.

	n	ApoE3	TC	TG
			mg/dl	
MALE				
Nontransgenic	4	0	26 ± 5	42 ± 27
ApoE3 low (<10 mg/dl)	6	8 ± 2	37 ± 18	26 ± 15
ApoE3 medium (10–20 mg/dl)	5	15 ± 4	109 ± 49[a]	72 ± 48
ApoE3 high (>20 mg/dl)	6	28 ± 4	224 ± 73[b]	198 ± 74[b]
FEMALE				
Nontransgenic	4	0	38 ± 8	31 ± 6
ApoE3 low (<10 mg/dl)	4	8 ± 1	49 ± 6	25 ± 9
ApoE3 medium (10–20 mg/dl)	3	14 ± 4	108 ± 40[a]	83 ± 54
ApoE3 high (>20 mg/dl)	3	29 ± 2	182 ± 26[b]	154 ± 33[b]

[a] $p < 0.05$ *versus* nontransgenics.

[b] $p < 0.005$ *versus* nontransgenics.

FIG. 15